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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,750	TISCHER ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *95-124* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *95-124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 December 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *IUBMB printout*.

DETAILED ACTION

Status of the Application

Claims 95-124 are pending.

Applicant's cancellation of claims 1, 27, 33, 46-94, addition of new claims 95-124, amendments to the specification, and a copy of the entry EC 5.4.2.7, as submitted in a communication filed on 5/22/2006 are acknowledged.

All previously examined claimed have now been cancelled. New claims 95-124 are deemed directed to the elected subject matter and find support in the originally filed claims. Claims 95-124 are at issue and are being examined herein.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Specification

1. The specification remains objected to in view of the lack of clarity regarding the definition of percent identity as shown on page 13, lines 6-8. As previously indicated, the definition of the term "n" as shown in the specification as originally filed is unclear and confusing. Applicant has amended the specification in response to the objection made in the Non Final action mailed on 2/21/2006. However, the amendment of the term "n" results in the definition of percent identity to be unrelated to the definition of percent identity as commonly understood in the art. As amended, the term "n" has been defined as "the difference between the number of nucleotides or amino acids of the selected sequence and that of the basic sequence". Percent identity has been originally defined as $I = nx100/L$, where L is the length of the basic sequence. Due to the amended definition of "n", it appears that percent identity is only dependent upon the length of the two sequences being compared, whereas one of skill in the art would understand percent identity to be dependent upon how many nucleotides/amino acids are the same at a particular position in a sequence. One of skill in the art would have understood the term "n" to represent the

number of nucleotide/amino acid matches between two sequences. As currently defined, percent identity increases if the differential in length between the two sequences being compared increases. For example, using the current definition of "n", if the basic sequence is 100 nucleotides long, and the sequence being compared to the basic sequence is 200 nucleotides long, then the percent identity between the two sequences is 100% (100% = (200-100)x100/100). Clarification is required.

2. The specification as amended is objected to due to the recitation of "EC 2.7.5.6" for the following reasons. While it is clear to the Examiner that a typographical error has been made with regard to the recitation of "EC 2.7.5.1" next to the term "deoxyribomutase" in the specification as originally filed since that EC number does not correspond to an enzyme having deoxyribomutase activity (also indicated by the Examiner in the Non Final action mailed on 2/21/2006; page 5,item 14), Applicant's amendment changing the term "EC 2.7.5.1" to "EC 2.7.5.6" next to the term "deoxyribomutase" is unclear and confusing in view of the fact that as indicated by Applicant in the response, the current EC number associated with deoxyribomutase is "EC 5.4.2.7" and not "EC 2.7.5.6". As indicated by the Examiner in the previous Non Final action, and also shown in Applicant's submission of EC 5.4.2.7, the term "deoxyribomutase" is an alternative name for "phosphopentomutase". As shown in the IUBMB enzyme nomenclature printout submitted with the instant Office action, EC 2.7.5.6 was deleted in 1984 and is currently not assigned to any enzyme. The Examiner acknowledges that prior to 1984, the EC number associated with deoxyribomutase was EC 2.7.5.6. However, that number is no longer in use and was not used even at the time of filing of the priority documents of the instant application. Appropriate correction is required.

Claim Objections

3. Claim 95 is objected to due to the recitation of "substrate phosphorylation of said inorganic phosphate with a substrate" for the following reasons. As known in the art, phosphorylation results in a

phosphate group being added to a substrate. As written, substrate phosphorylation would only yield PP_i (phosphorylation of inorganic phosphate). However, it is clear from other claims, such as claims 100-104, that the intended meaning of the term is the phosphorylation of a variety of substrates with the inorganic phosphate. While the Examiner has interpreted the term to recite "substrate phosphorylation of a substrate with said inorganic phosphate", the claim should be amended to clearly indicate that the intended limitation is the removal of inorganic phosphate by phosphorylation of a substrate with the inorganic phosphate.

4. Claim 103 is objected to due to the recitation of "the method of claim 102, wherein the phosphate transfer" for the following reasons. While the phosphorylation step in claim 102 encompasses phosphate transfer, for consistency and clarity, it is suggested that the term "phosphate transfer" be replaced with "substrate phosphorylation".

5. Claim 115 is objected to due to the recitation of "nucleotide sequence hybridizing under stringent conditions to the complementary sequence of....." for the following reasons. A nucleotide sequence is a graphical representation of the order in which nucleotides are arranged in a nucleic acid molecule. Hybridization occurs between nucleic acid molecules. While the Examiner has interpreted the term "nucleotide sequence hybridizing...to.....sequence" to read "polynucleotide which hybridizes to ...polynucleotide", it is suggested the claim be amended to clearly indicate that polynucleotides and not sequences are hybridizing.

Claim Rejections - 35 USC § 112, Second Paragraph

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. New claims 106, 115, 117, 121-123 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by amendment.

8. Claim 106 is indefinite in the recitation of "deoxyribomutase (EC 2.7.5.6) or a phosphopentose mutase (PPM, EC 5.4.2.7)" for the following reasons. As indicated in the Non Final action mailed on 2/21/2006, the term "deoxyribomutase" is an alternative name for phosphopentomutase, which corresponds to EC 5.4.2.7. See also Applicant's own submission of EC 5.4.2.7 filed on 5/22/2006. Therefore, it is unclear as to whether Applicant considers the enzymatic activity of a deoxyribomutase to be different from that of a phosphopentomutase even though the art considers the enzymatic activity of a deoxyribomutase and a phosphopentomutase to be equivalent. It is also noted that the term "deoxyribomutase (EC 2.7.5.6)" is unclear since the EC number which corresponds to a deoxyribomutase is EC 5.4.2.7. As previously discussed, while EC 2.7.5.6 was the number assigned to a deoxyribomutase, it was deleted in 1984 (several years prior to filing of the priority documents of the instant application), and has not been assigned to a different enzyme. See attached IUBMB enzyme nomenclature printout. For examination purposes, it will be assumed that the claim reads "the method of claim 105, comprising isomerizing said deoxyribose-5-phosphate with a phosphopentomutase (PPM, EC 5.4.2.7)".

9. Claim 115 is indefinite in the recitation of "stringent conditions" as it is unclear which polynucleotide is being recited absent a statement of the conditions under which the hybridization reaction is performed. As indicated in the Non Final action mailed on 2/21/2006, nucleic acids which will hybridize under some hybridization conditions will not necessarily hybridize under different conditions. It is reiterated herein that while the specification exemplifies several conditions (buffer and temperature) as stringent (page 12, lines 22-26), there is no definition of what constitutes "stringent conditions". For examination purposes, it will be assumed that the term refers to hybridization under any conditions.

10. Claim 117 is indefinite in the recitation of "the method of claim 116 wherein the reaction is carried out without isolating intermediate products" because it is unclear as to which reaction should be carried out without isolating intermediate products. Steps (i)-(iii) can all be reactions (i.e., condensation, isomerization, and dephosphorylation reactions). It is unclear as to whether the term "the reaction" refers to all the reactions in the method or if it refers to a specific one. For examination purposes, it will be assumed that it refers to step (iii).

11. Claim 121 and 123 are indefinite in the recitation of "wherein said excess starting materials or by-products are selected form the group consisting of fructose 1,6-diphosphate and deoxyxylulose-1-phosphate (dX1P)" for the following reasons. Neither claim 116, 120 or 122 require as a starting material fructose 1,6-diphosphate or deoxyxylulose-1-phosphate. The first step in the claimed method requires condensation of GAP with acetaldehyde. Thus, one of skill in the art would assume that the starting materials are GAP and acetaldehyde. It is also not known in the art, or disclosed in the specification, that fructose 1,6-diphosphate or deoxyxylulose-1-phosphate are byproducts of any of the reactions of steps (i)-(iii) recited in claim 116. Thus, it is unclear as to how claims 121 and 123 further limits claims 120 and 122. For examination purposes, claims 121 and 123 will be considered duplicates of claims 120 and 122, respectively.

12. Claim 122 is indefinite in the recitation of "wherein no substantial amounts of starting materials..." for the following reasons. The term "substantial" is a relative term and neither the specification nor the claim provides a definition or a standard for ascertaining the requisite degree such that one of skill in the art would be reasonably apprised of the scope of the invention. For examination purposes, it will be assumed that the term "no substantial amounts" reads "no amount".

Claim Rejections - 35 USC § 112, First Paragraph

13. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

14. New claims 95-124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is necessitated by amendment.

15. Applicant argues that the claims have been amended such that they no longer cover any pathway which would produce a deoxyribonucleoside nor a method catalyzed by any enzyme.

16. Applicant's arguments have been fully considered but are not deemed persuasive to avoid the rejection of new claims 95-124. With regard to claims 95-115, while it is agreed that new claims 95-115 now require an enzyme to catalyze the reaction between dR1P and a nucleobase to produce a genus of deoxyribonucleosides, i.e., purine nucleoside phosphorylase, it is noted that while the claimed method encompasses the synthesis of any deoxyribonucleoside, as known in the art, purine nucleoside phosphorylases are specific with regard to the nucleobase such that it is unlikely that one of skill in the art can obtain pyrimidine deoxyribonucleosides using a purine nucleoside phosphorylase. Pugmire et al. (Biochem. J. 361:1-25, 2002) teach that the art recognizes two separate types of nucleosidases (another name for nucleoside phosphorylases): one specific for purines and another specific for pyrimidines (page 1, last sentence of left column). The specification fails to disclose the structures of purine nucleoside phosphorylases which would catalyze a reaction that would produce pyrimidine deoxyribonucleosides. In addition, the claims also encompass producing deoxyribonucleosides comprising a particular nucleobase from deoxyribonucleosides having a different nucleobase (claims 111-115) by any means (e.g., chemical and enzymatic). While the specification discloses a *L. leichmannii* nucleoside 2-deoxyribosyl transferase

encoded by the polynucleotide of SEQ ID NO: 13 and a process catalyzed by said nucleoside 2-deoxyribosyl transferase where a deoxyribonucleoside having a particular nucleobase is produced from another deoxyribonucleoside having a different nucleobase, the specification is silent in regard to other methods to obtain said deoxyribonucleoside, such as chemical synthesis and the conditions/catalysts required, additional nucleoside 2-deoxyribosyl transferases, or the structural elements found in the *L. leichmannii* nucleoside 2-deoxyribosyl transferase disclosed in the specification required in any nucleoside 2-deoxyribosyl transferase.

With regard to claims 116-124, it is noted that while the preamble of claim 116 refers to the *in vitro* enzymatic synthesis of deoxyribonucleosides, the steps required do not have to be enzymatically catalyzed. The synthesis of deoxyribonucleosides can encompass additional steps not recited in the claims (e.g., synthesis of additional precursors). Only one step is required to be enzymatically catalyzed to meet the limitation in the preamble and that step is not required to be any of those recited in the claim. Thus, as written, the claimed method encompasses in part the steps recited in the claims carried out under any conditions (i.e., non-enzymatic) and additional steps catalyzed by any enzyme.

As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The instant claims require an extremely large genus of enzymes and/or chemical catalysts for which the specification provides no adequate description. As previously indicated in the Non Final action mailed on 2/21/2006, while the specification discloses the enzymatic synthesis of deoxyadenosine from dR1P with an *E. coli* purine nucleoside phosphorylase, and the art teaches the enzymatic synthesis of deoxyribonucleosides from dR1P with purine and thymidine phosphorylases (Tozzi et al., FEBS Journal 273:1089-1101, 2006, Figure 1, pages 1089-1090; Bzowska et al., Pharmacology & Therapeutics 88:349-425, 2000, page 351, left column, first sentence, page 411; Pugmire et al., pages 1-2; Barbas et al. and Yamauchi et al. cited in the previous Office action), the specification is silent with regard to other enzymes which would catalyze the synthesis of deoxyribonucleosides from dR1P or the synthesis of any precursor of a deoxyribonucleoside, the chemical catalysts which would catalyze the synthesis of any precursor of a deoxyribonucleoside or those recited in the claims (i.e., dR5P and dR1P), or the conditions required for chemical synthesis of these precursors.

Thus, in view of the teachings of the specification and the art, as well as the lack of description of additional species within the genus of enzymes, chemical catalysts, and/or methods encompassed by the claims by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

17. New claims 95-124 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a method for *in vitro* enzymatic synthesis of purine deoxyribonucleosides wherein said method comprises reacting deoxyribose 1-phosphate (dR1P) and a nucleobase in the presence of a purine nucleoside phosphorylase, (2) a method for *in vitro* enzymatic synthesis of deoxyribonucleosides wherein said method comprises reacting deoxyribose 1-phosphate (dR1P) and a nucleobase in the presence of a purine nucleoside phosphorylase or a thymidine phosphorylase, or (3) the method of (1) or (2) further comprising reacting the deoxyribonucleosides with a different nucleobase in

the presence of the *L. leichmannii* nucleoside 2-deoxyribosyl transferase encoded by the polynucleotide of SEQ ID NO: 13 to obtain different deoxyribonucleosides, does not reasonably provide enablement for (a) a method for the *in vitro* enzymatic synthesis of a pyrimidine deoxyribonucleoside wherein said method comprises reacting deoxyribose 1-phosphate (dR1P) and a nucleobase in the presence of a purine nucleoside phosphorylase, (b) a method for the *in vitro* enzymatic production of any deoxyribonucleoside wherein said method requires any enzyme which would catalyze any step in the synthesis of a deoxyribonucleoside, and also requires specific steps which may not be enzymatically catalyzed, or (c) the method of (a) or (b) further comprising reacting the deoxyribonucleoside with a different nucleobase to obtain a new deoxyribonucleoside by any method or by enzymatic synthesis using any nucleoside 2-deoxyribosyl transferase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection is necessitated by amendment.

18. Applicant argues that the claims have been amended such that they no longer cover any pathway which would produce a deoxyribonucleoside nor a method catalyzed by any enzyme.

19. Applicant's arguments have been fully considered but are not deemed persuasive to avoid the rejection of new claims 95-124. With regard to claims 95-115, as indicated above, while the Examiner acknowledges that new claims 95-115 now require a purine nucleoside phosphorylase to catalyze the reaction between dR1P and a nucleobase, the claims are also directed in part to a method to enzymatically produce pyrimidine deoxyribonucleosides. Based on the teachings of the art, as evidenced by Pugmire et al., one of skill in the art would reasonably conclude that it is unlikely that pyrimidine deoxyribonucleosides can be enzymatically synthesized by reacting dR1P and a nucleobase in the presence of a purine nucleoside phosphorylase in view of the fact that nucleoside phosphorylases are specific for either purines or pyrimidines. See the teachings of Pugmire et al. discussed above. In addition, there is no disclosure in the specification as to purine nucleoside phosphorylases which can be

used to produce pyrimidine deoxyribonucleosides or which are the structural elements required in a purine nucleoside phosphorylase to use pyrimidines as substrates. Also, as previously stated, while the claims further require a step wherein the deoxyribonucleosides obtained from the reaction catalyzed by a purine nucleoside phosphorylase are reacted in the presence of a different nucleobase to produce different deoxyribonucleosides by any method, the specification is completely silent with regard to (1) chemical catalysts and conditions which would allow the chemical synthesis of these deoxyribonucleosides, (2) other enzymes which would catalyze the required reaction with the exception of a *L. leichmannii* nucleoside 2-deoxyribosyl transferase encoded by the polynucleotide of SEQ ID NO: 13, or (3) the structural elements found in the *L. leichmannii* nucleoside 2-deoxyribosyl transferase disclosed which are required in any nucleoside 2-deoxyribosyl transferase. As discussed in the Non Final action mailed on 2/21/2006, the art teaches the unpredictability of assigning function based solely on structural homology and how even minor structural changes have an effect on function. See the teachings of Witkowski et al., Seffernick et al., and Branden et al. Therefore, in view of the amount of information provided by the specification, the absence of information as to the structure of purine nucleoside phosphorylases that would catalyze the synthesis of pyrimidine deoxyribonucleosides, the lack of guidance as to how to obtain deoxyribonucleosides having different nucleobases as recited in the claims by chemical synthesis or using other enzymes, the lack of a correlation between structure and nucleoside 2-deoxyribosyl transferase activity, the lack of information as to the general tolerance of nucleoside 2-deoxyribosyl transferases to structural modifications and the extent of such tolerance, and the unpredictability of the art regarding structural variation and function, one of skill in the art would have to conclude that undue experimentation is required to practice the full scope of the instant claims.

As previously discussed with regard to claims 116-124, the claims as written do not require any of the steps recited to be enzymatically catalyzed. See extensive discussion above about the scope of these claims. Thus, the method of claims 116-124 partially encompasses the steps recited in the claims

carried out under any conditions (i.e., non-enzymatic) and additional steps catalyzed by any enzyme. The enablement provided is not commensurate in scope with the claims due to the extremely large number of unknown enzymes and/or conditions required in the claimed method. While the specification discloses the enzymatic synthesis of deoxyadenosine from dR1P with an *E. coli* purine nucleoside phosphorylase, and the enzymatic synthesis of deoxyribonucleosides from dR1P with purine and thymidine phosphorylases is well known in the art, the specification fails to disclose (1) other enzymes which would catalyze the synthesis of deoxyribonucleosides from dR1P, (2) all the enzymes which catalyze the synthesis of any precursor of a deoxyribonucleoside, (3) the chemical catalysts which would catalyze the synthesis of the recited precursors (i.e., dR1P and dR5P) or any precursor of a deoxyribonucleoside, or (4) the conditions required for chemical synthesis of these precursors. It is not routine in the art to screen by a trial and error process for all enzymes which can catalyze the synthesis of any precursor of a deoxyribonucleoside, or all the conditions/chemical catalysts which would allow any precursor of a deoxyribonucleoside to be synthesized. In the absence of some guidance as to which conditions/catalysts/enzymes would allow the synthesis of any precursor of a deoxyribonucleoside, one of skill in the art would have to test an essentially infinite number of compounds/enzymes/conditions to enable the full scope of the claims. Thus, Applicant has not provided sufficient guidance for one of skill in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 103

20. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

21. Claims 1, 27, 33, 46-49, 75-84 were rejected under 35 U.S.C. 103(a) as being unpatentable over Yamauchi et al. (EP 0411158 B1, published on May 29, 1996; cited in the IDS and the restriction

requirement) in view of Baranov et al. (EP 0593757 B1, published on 1/15/1997). In view of applicant's amendment canceling claims 1, 27, 33, 46-49, 75-84, this rejection is hereby withdrawn.

22. Claims 1, 27, 33, 46-48, 59-64, 75-84 were rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, C. (Ph.D. Thesis, Texas A&M University, 1989; cited in the specification) in view of Baranov et al. (EP 0593757 B1, published on 1/15/1997). In view of applicant's amendment canceling claims 1, 27, 33, 46-48, 59-64, 75-84, this rejection is hereby withdrawn.

23. Claims 50 and 53 were rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, C. (Ph.D. Thesis, Texas A&M University, 1989; cited in the specification) in view of Baranov et al. (EP 0593757 B1, published on 1/15/1997), and further in view of DeFrees et al. (WO 96/32491 published 10/17/1996). In view of applicant's amendment canceling claims 50 and 53, this rejection is hereby withdrawn.

24. Claims 50 and 53 were rejected under 35 U.S.C. 103(a) as being unpatentable over Yamauchi et al. (EP 0411158 B1, published on May 29, 1996; cited in the IDS and the previous Office Action) in view of Baranov et al. (EP 0593757 B1, published on 1/15/1997), and further in view of DeFrees et al. (WO 96/32491 published 10/17/1996). In view of applicant's amendment canceling claims 50 and 53, this rejection is hereby withdrawn.

25. It is noted that new claims 95-104 are not being rejected as being unpatentable over Yamauchi et al. in view of Baranov et al., and new claims 95-110 are not being rejected as being unpatentable over Barbas in view of Baranov et al. due to the fact that none of these references alone or in combination teach or suggest removal of inorganic phosphate by phosphorylation of a substrate with said inorganic phosphate, which is a limitation required by the claims. Furthermore, the Examiner has been unable to find motivation in the prior art for removal of inorganic phosphate by phosphorylation of a substrate in a method for producing deoxyribonucleosides as claimed. As indicated in the Non Final action of 2/21/2006, the Examiner was unable to find motivation in the prior art for removal of inorganic phosphate

by reacting inorganic phosphate with fructose diphosphate or with a polysaccharide. Applicant has not submitted references which would have provided motivation for one of skill in the art to remove inorganic phosphate by reacting said inorganic phosphate with fructose diphosphate/polysaccharides in their response filed on 5/22/2006. Applicant maintains in their response filed on 5/22/2006 that the cited art does not teach or indicate that inorganic phosphate can be removed by substrate phosphorylation.

26. Claims 116-118, 120-124 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, C. (Ph.D. Thesis, Texas A&M University, 1989; cited in the specification) in view of Baranov et al. (EP 0593757 B1, published on 1/15/1997). This rejection has been discussed at length with regard to now canceled claims 1, 27, 33, 46-48, 59-64, 75-84 and is now applied to new claims 116-118, 120-124 for the reasons of record.

27. Applicant argues that the claims have been amended to indicate that the method of claim 95 involves elimination of the inorganic phosphate by substrate phosphorylation. Applicant maintains that this limitation is not taught or suggested by the cited prior art.

28. Applicant's arguments have been fully considered but are not deemed persuasive with regard to new claims 116-118, 120-124. New claims 116-118, 120-124 do not require elimination of inorganic phosphate by substrate phosphorylation. Claim 116 is directed to a method for the *in vitro* enzymatic synthesis of deoxyribonucleosides which comprises three steps: (i) condensing GAP with acetaldehyde to form dR5P, (ii) isomerizing dR5P to dR1P, and (iii) reacting dR1P and a nucleobase to form a deoxyribonucleoside and inorganic phosphate. Claim 117 as interpreted is directed to the method of claim 116 wherein the reaction in step (iii) is carried out without isolating intermediate products. Claim 118 adds an additional step to the method of claim 116 regarding the formation of GAP from FDP, DHA or GP. Claims 120-121 as interpreted are directed in part to the method of claim 116 wherein by-products of step (i) are removed prior to step (ii). Claims 122-123 as interpreted are directed in part to the method

of claim 116 wherein no by-products are present prior to step (ii). Claim 124 is directed to the method of claim 116 wherein inorganic phosphate produced in step (iii) is removed. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation.

As previously indicated in the Non Final action, Barbas, as admitted in the specification (page 2, lines 8-24), teaches the synthesis of deoxyribonucleosides wherein dR1P and a nucleobase are combined in a reaction catalyzed by thymidine phosphorylase and wherein dR1P is produced by isomerizing dR5P in a reaction catalyzed by phosphopentomutase (Barbas, pages 48-53; Scheme III in page 58). The nucleobase in Scheme III is thymidine. Barbas does not isolate any intermediate products from the reaction between dR1P and the nucleobase (step (iii)). Barbas also teaches (1) the cloning and production of fructose 1,6-biphosphate aldolase from *C. glutamicum* and *E. coli* (pages 70-84), (2) discloses that this enzyme catalyzes the reversible aldol condensation of DHAP and G3P (also called GAP) to produce fructose 1,6-biphosphate (page 65, first complete paragraph), (3) discloses the use of aldolases in the synthesis of useful compounds as well as the combined use of aldolases and isomerases for the production of unusual sugars (pages 64-67; Figure 25), and (4) teaches the production of 2-deoxyribose-5-phosphate (dR5P) from GAP and acetaldehyde in a reaction catalyzed by a deoxyribose-5-phosphate aldolase (page 88, second paragraph). Barbas does not teach a single continuous process to produce deoxyribonucleosides wherein fructose 1,6-biphosphate is converted to GAP, GAP and acetylaldehyde are reacted to produce dR5P, dR5P is isomerized to dR1P, and dR1P and a nucleobase are reacted to produce a deoxyribonucleoside. Also, Barbas does not teach removal of inorganic phosphate formed in a reaction between dR1P and a nucleobase. Baranov et al. teach a method for obtaining polypeptides in a cell-free system and teach the removal of inorganic phosphate and inorganic pyrophosphate from the system to allow the continuous production of the desired product (page 2, second column, lines 11-26). Baranov et al. do not teach a method for the production of deoxyribonucleosides.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to remove the inorganic phosphate (as taught by Baranov et al.) which results from the synthesis of deoxyribonucleosides, as taught by Barbas. Also, it would have been obvious to modify the method of Barbas (which already contains two of the consecutive steps required) to obtain a method which further comprises two additional steps: (1) the enzymatic production of GAP from FDP in a reaction catalyzed by an FDP (fructose diphosphate) aldolase, and (2) the enzymatic production of dR5P from GAP in a reaction catalyzed by a phosphopentose mutase. A person of ordinary skill in the art is motivated to (1) remove inorganic phosphate for the benefit of driving the reaction between dR1P and the nucleobase towards synthesis of the deoxyribonucleoside, and (2) add steps to the method of Barbas to enzymatically produce the precursors dR5P and GAP (precursors of dR1P) since (i) it is well known in the art that enzymatic processes are more specific in regard to the substrates and products, therefore having the potential of being more efficient than chemical synthesis, and (ii) a process where FDP is the starting material is more cost effective since FDP is less expensive than dR5P. One of ordinary skill in the art has a reasonable expectation of success at removing inorganic phosphate and producing the dR1P precursors enzymatically since removal of inorganic phosphate is well known in the art and the enzymatic synthesis of dR5P and GAP is disclosed by Barbas. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

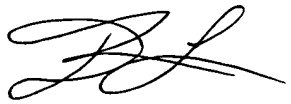
29. No claim is in condition for allowance.

30. Applicant's amendment introducing new claims necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

31. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.



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DR
August 6, 2006